ethylenediaminetetraacetic acid-5, 0.1% bovine serum albumin) either alone or with 5 μmol/l of the V_{1A} selective blocker SR49059. Incubation was at 25°C for 2 h in a volume of 100 μl, and steady-state kinetics were achieved in specific binding. The reaction was terminated with ice-cold incubation buffer and rapid vacuum filtration through glass fiber filters. Each filter was washed 3× with 7 ml of ice-cold 10 mmol/l Tris-hydrochloric acid plus 0.1% bovine serum albumin. Radioactivity was determined in a Gamma counter. All assays were performed in duplicate. Receptor density was normalized to membrane protein. The dissociation constant (κ_d) and the maximal number of binding sites (B_{max}) for ^{125}I-p-AVP were determined by Scatchard analysis of saturation binding isotherms with Graphpad Prism (GraphPad, San Diego, California). Nonspecific binding was 30% and was subtracted from total binding. When using the radio-labeled antagonist specific for V_{1A}-R (κ_d 30 pmol for human recombinant V_{1A}-R), all Scatchard plots were linear, and the binding curves fit a 1 binding site model.

As seen in Figure 1, the density of V_{1A}-R was significantly increased in failing hearts when compared with nonfailing heart control subjects without any change in the affinity of the ligand for the receptor. That the change in density was due to an increase in receptor expression was supported by the fact that there was a comparable increase in the levels of the messenger ribonucleic acid encoding V_{1A}-R (Fig. 1). This represents the first report demonstrating changes in V_{1A}-R expression in HF. The majority of the patients were receiving inotropic therapy, and therefore our findings might not be generalizable to patients with less severe disease. Interestingly, our findings are in contrast with the decrease in the expression of β_1-adrenergic and angiotensin type 1 receptors that characterize the failing human heart (4). Further studies will be required to better understand the molecular mechanisms responsible for this difference as well as to determine whether these changes in receptor density contribute to diminished cardiac function observed in patients with end-stage HF and elevated the levels of AVP.

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Letters to the Editor

Same-Day Discharge After Percutaneous Coronary Intervention

Trial Sequential Analysis of Outcomes

In the comparison made between same-day discharge and routine overnight observation by Brayton et al. (1), the best level of evidence was that derived from randomized controlled trial (RCT) studies. With regard to the composite outcome of death, myocardial infarction, or target lesion revascularization, the analysis of 7 RCTs showed no significant differences between the 2 approaches (pooled odds ratio: 0.90; 95% confidence interval: 0.43 to 1.87; $p = 0.78$). While this result supports the conclusion of no proven difference, the main question is whether or not the available data support a conclusion in terms of proof of no difference (or proof of noninferiority) rather than the mere demonstration of no proof of difference.

One problem in exploring these methodological questions is that the degree of consensus on how noninferiority meta-analysis can be conducted is still modest (2). On the other hand, the advantages of trial sequential analysis (TSA) are being recognized increasingly not only for handling questions of superiority (3,4) but also with regard to those of noninferiority (3–5); in fact, TSA aims at classifying each meta-analysis into one of only 4 categories (superiority, inferiority, futility/noninferiority, inconclusive result).

We applied TSA to the same 7 RCTs examined by Brayton et al. (1). Our assumptions included 2-sided testing, type 1 error of 5%, and a power of 80%. With respect to the above-mentioned composite outcome, the intervention effect was set at a relative risk reduction (RRR) of 50% or 33%. The expected absolute event rate in the controls was 7.6% (i.e., the cumulative arithmetic rate in the control groups of the 7 RCTs). The main result of TSA was expressed through the graph of a cumulative z-curve; the boundaries in this graph for concluding superiority or inferiority or futility were determined according to the O'Brien–Fleming alpha-spending function. All calculations were carried out using a specific statistical software (User Manual for TSA, TSA, Copenhagen Trial Unit 2011).

Our results are shown in Figure 1. The number of events recorded in the RCTs proved to be insufficient to construct the boundaries of futility in both analyses; in addition, the statistical procedure incorporated only 6 RCTs because one trial

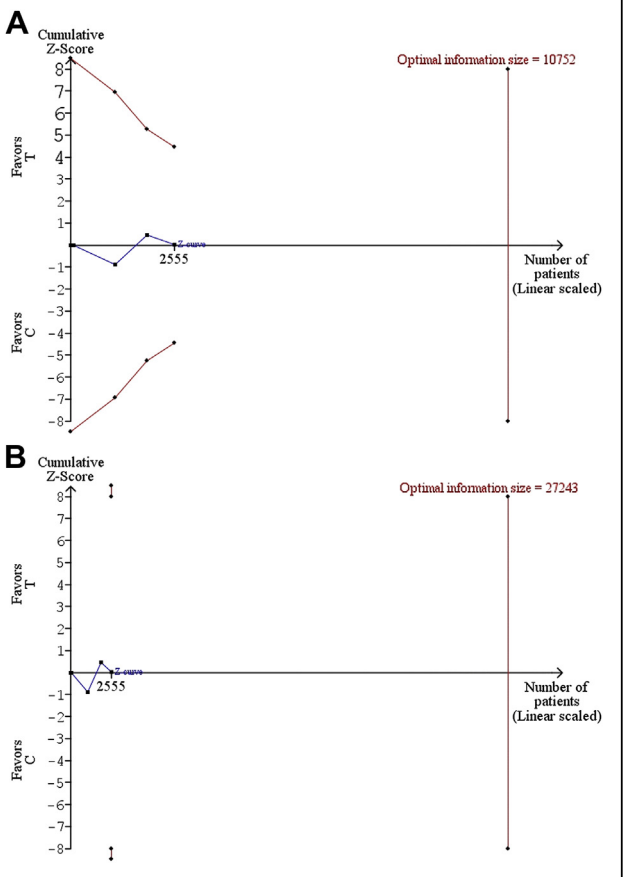

Figure 1 **Trial Sequential Analysis of 6 RCTs Comparing Same-Day Discharge With Routine Overnight Observation After Percutaneous Coronary Intervention**

The expected relative risk reduction (RRR) was assumed to be 50% **(A)** or 33% **(B)**. In the z-curve **(blue)**, individual trials correspond to individual segments; trials are plotted in chronological order **(from left to right)**. The x-axis indicates the cumulative number of patients; the starting point of the z-curve is always at x = 0, that is, inclusion of no trials. C = control arm (routine overnight observation); RCT = randomized controlled studies; T = treatment arm (same-day discharge); **red lines** are the boundaries for superiority or inferiority.

(characterized by zero-event frequency in both arms) was uninformative according to the TSA statistical algorithm.

Our results indicate that current information from RCTs does not allow us to draw any firm conclusion about the outcome comparison between the two approaches (i.e., "inconclusive result" of TSA). In fact, while the overall number of patients enrolled in the 6 trials was 2,555, our TSA estimated that the optimal information size would be 10,752 patients (assuming RRR = 50%) or 27,243 patients (assuming RRR = 33%).

In summary, the number of patients studied in the RCTs presently available is only one-fourth or one-tenth in comparison with the ideal sample size required to draw a firm conclusion. Therefore, the comparison between the 2 discharge strategies remains open.

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Statistical Uncertainty in 10-Year Framingham Risk of Coronary Heart Disease and Cardiovascular Disease

In a recent study, Ford (1) presents an important analysis, with implications for public health prioritization. However, we believe some of the findings should be interpreted with caution. The Framingham Heart Study has contributed immeasurably to our understanding of cardiovascular disease in the United States and internationally, but the published regression equations for 10-year risk of coronary heart disease (CHD) and cardiovascular disease (CVD) were developed for clinical use, and variance-covariance matrices were not reported (2,3). Thus, it is impossible to quantify uncertainty or estimate confidence intervals for any patient's 10-year risk of CHD or CVD. In other words, while the mean of the risk is known, its variance is unknown.

For this reason, the standard errors for the population-level 10-year risk of CHD and CVD that Ford (1) presents in Table 1 in his article are misleading. The same method is used to estimate these standard errors as used for measures such as age, blood pressure, and cholesterol level. The difference between them is that, unlike Framingham risk scores, these characteristics can be measured with certainty (or are assumed to be measured with negligible error and thus are treated as "certain"); thus, their standard errors are appropriate and accurate. On the other hand, the standard errors reported for population-level 10-year risk of CHD and CVD are inappropriate because they capture only between-person variability in predicted risk but do not account for the fact